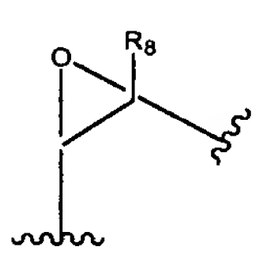
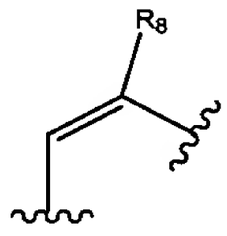
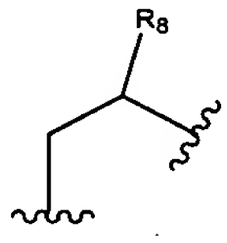
REMARKS

Claims 1-4, 7-8, and 11, as amended, and new claims 15-58 are pending in this application for the Examiner's review and consideration. Applicants appreciate the courtesies extended to Applicants' attorneys, Anthony M. Insogna and Paul E. Dietze, during a telephonic interview conducted on October 24, 2001. The comments appearing herein are substantially in accordance with those presented and discussed in the interview. Applicants appreciate the Examiners recognition of patentable subject matter in claims 3 and 14. Applicants note, however, that the Examiner alleged that claim 3 was a dependent claim. Claim 3, however, is an independent claim.

The specification was amended to correct typographical errors. Specifically, the specification was amended to correct typographical errors wherein some of the cancers itemized in the list of representative cancers that can be treated with the compounds of the invention, on pages 8 and 9 of the specification, were listed more than once.

Claims 5-6, 9-10, and 12-13 were canceled without prejudice pursuant to a restriction requirement. During the interview the Examiner restricted these claims into three groups, Group I, claims 4, 7, 8, and 11 drawn to methods of treating cancer; Group II claims 5, 9, and 12, drawn to methods of treating a hyperprolferative cellular disease in a patient; and Group III claims 6, 10, and 13 drawn to methods of treating a disease associated with angiogenesis in a patient. Applicants elect the claims of Group I for examination in this application and, accordingly, have canceled without prejudice the claims of Group II and Group III. Applicants reserve the right to file one or more divisional or continuation applications directed to the subject matter of the canceled claims or other unclaimed subject matter.

Claims 1 was amended to more particularly and distinctly recite the invention. Specifically claim 1 was amended to recite that Q is: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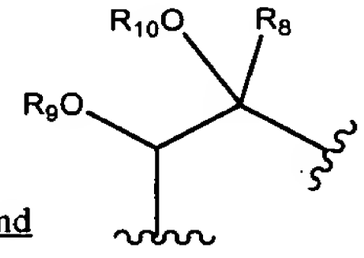
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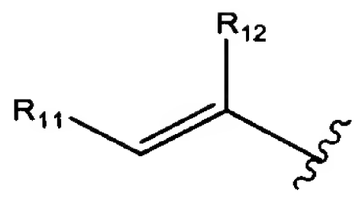
that G is is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;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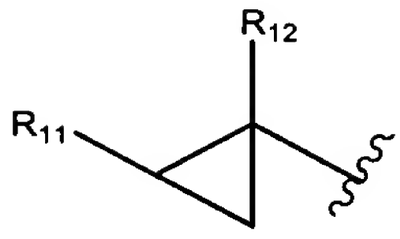
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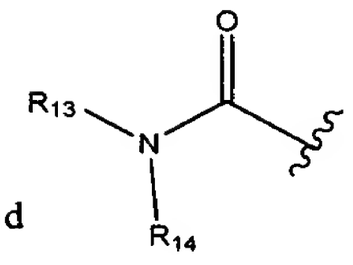
and

.

Claim 1 was further amended to recite that Z_1 and Z_2 are both CH_2. Claim 4 was amended to recite --cancer-- instead of "carcinoma" (*See e.g.*, Specification, page 8, lines 20-23). Claim 8 was amended to recite specific cancers that are known to be treated by microtubule-stabilizing agents, such as Taxol®. Claim 14 was amended to recite that the claimed compound also includes pharmaceutically acceptable salts, hydrates, solvates, geometrical isomers, optical isomers, or stereoisomers thereof (*See e.g.*, Specification, page 3, line 18, page 8, lines 14-16, and page 11, lines 1-3).

New claims 15 and 16 depend from claim 14 and recite methods of treating cancers that are known to be treated by microtubule-stabilizing agents, such as Taxol®. New claim 17 and 18 depend from claim 8 and recite methods of treating cancers that are known to be treated by microtubule-stabilizing agents, such as Taxol®. New claims 19-22 depend from claim 1 and recite preferred embodiments of the compound of claim 1. New claims 23-30 recite methods of treating cancers by administering to a patient a therapeutically effective amount of one of the preferred compounds recited in claims 19-22. New claims 31-38 recite a method of treating a cancer responsive to microtubule stabilization by administering to a patient a therapeutically effective amount of a compound of claim 1-3, 14, 19-22, respectively (*See e.g.*, Specification, page 1, lines 11-21). New claims 39-42 depend from claim 4 and recite that the method further comprises administering one or more additional anti-cancer agents (*See e.g.*, Specification, page 10, lines 10-29). New claims 43- 50 recite pharmaceutical compositions that include the compounds of claims 1-3, 14, and 19-22, respectively (*See e.g.*, Specification, page 11, lines 4-8). New claims 51-58 recite methods of treating specific cancers that are known to be treated by microtubule-stabilizing agents, such as Taxol® (melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma) by administering to a patient a therapeutically effective amount of one of the preferred compounds recited in claims 1-3, 14, and 19-22, respectively. No new matter has been added by these claim amendments and new claims so that their entry at this time is warranted.

THE INVENTION

Epothilones are a class of microtubule-stabilizing agents with a Taxol®-like mechanism of action. [D.M. Bollag, *Exp. Opin. Invest. Drugs* (1997), 6(7): 867-873 ("Bollag")]. Since the introduction of epothilones into the art, many groups have been designing, synthesizing, and testing epothilones. [D. Schinzer et al., *Angew. Chem. Int. Ed. Engl.*, 1997, 36, No. 3, 523-524; K.C. Nicolaou, et al., *J. Amer. Chem. Soc.*, 1997, 119, 7974-7991; K.C. Nicaloau et al., *Angew. Chem. Int. Ed. Engl.*, 1996, 35, No. 20, 2399-2401; A. Balog et al., *Angew. Chem. Int. Ed. Engl.*, 1996, 35, No. 23/24, 2801-2803]. Claims 1-3, 14, 19-22 of this application are directed to novel epothilone molecules wherein the structure of the 16-member cyclic epothilone ring or substituents attached to the 16-member cyclic epothilone ring are modified. Claims 4, 7-8, 11, 15-18, 23-30, 40-42, and 51-58 are directed to methods of treating cancer in a patient which comprises administering a therapeutically effective amount of a compound of the invention. Claims 31-38 are directed to methods of treating cancer responsive to microtubule stabilization which comprises administering a therapeutically effective amount of a compound of the invention. Claims 43-50 are directed to pharmaceutical compositions comprising a compound of the invention.

SUBMISSION OF INFORMATION DISCLOSURE STATEMENT

On September 28, 2001, Applicants filed an Information Disclosure Statement and List of References Cited by the Applicant in the above-identified application. The Information Disclosure Statement and List of References Cited by the Applicant, however, was filed after a Final Office Action had been issued in the case and, thus, was not entered. Since Applicants have now filed a Request for Continued Examination, it is respectfully requested that the Examiner enter into the record of this application the Information Disclosure Statement and List of References Cited by the Applicant that was filed on September 28, 2001 and to execute the List of References Cited by the Applicant to indicate consideration of these references.

THE REJECTION OF CLAIMS 1, 2, AND 4-13 AS BEING AN IMPROPER MARKUSH GROUP SHOULD BE WITHDRAWN

The Examiner rejected claims 1, 2, and 4-13 as being an improper Markush grouping for the reasons set forth on page 2 of the Office Action. The Examiner alleges that the variables W, G, Z_2, and Z_1 are defined in such a way that they keep changing the core of the compound that determines the classification. The rejection of claims 5-6, 9-10, and 12-13 are

rendered moot by the cancellation of these claims. With respect to claims 1, 2, 4, 7-8, and 11, as amended, Applicants respectfully traverse.

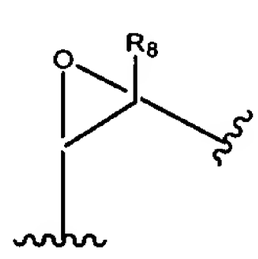
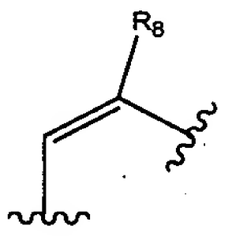
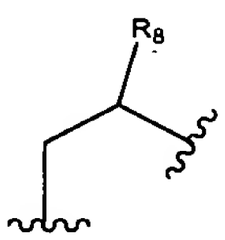
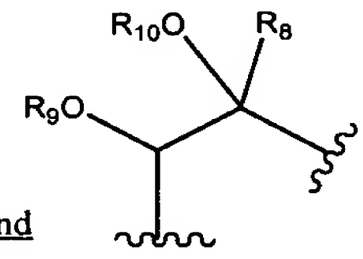
Applicants respectfully submit that this rejection is improper since the Examiner has not set forth any statutory basis (*e.g.*, under 35 U.S.C. §§ 101 or 112) for rejecting these claims. The proper action for addressing an improper Markush group is a restriction requirement. The claims, however, were not restricted by the Examiner before examination on the merits. Indeed, the Examiner has admitted that the subject matter of the invention is searchable by examining the claims on the merits. To now reject the claims, after a search and examination on the merits, as being drawn to an improper Markush group, is improper.

Furthermore, the Examiner's basis for the rejection is improper. Applicants respectfully submit that the compounds of Formula V are drawn to a proper Markush group. The MPEP states that "it is improper for the Office to refuse to examine that which the applicants regards as their invention unless the subject matter in a claim lacks unity of invention." MPEP 803.02. The MPEP goes on to state that "unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature as being essential to that utility." MPEP 803.02. The compounds of Formula V share a common utility, *i.e.*, they have utility as cytotoxic or mictotubule-stabilizing agents (*See, e.g.*, Victory et al. *Bioorg. and Med. Chem. Letters*, (1996), 6(7): 893-898 at page 898 and D.M. Bollag *Exp. Opin. Invest. Drugs* (1997), 6(7):867-873, at page 870) which is accepted and recognized in the art as a useful activity for a pharmaceutical. The compounds of Formula V also share a substantial structural feature that is essential to that utility, *i.e.,* they are in the class of 16-member ring macrolides. Applicants note that a Markush type claim can even include independent and distinct inventions, as long as they (1) share a common utility and (2) share a substantial structural feature as being essential to that utility. MPEP 803.02. Accordingly, Applicants respectfully submit that the compounds embraced by Formula V, *i.e.*, those recited in claims 1, 2, 4, 7-8, and 11 do constitute a proper Markush group.

Applicants further note that the Markush form of claiming allows the use of an artificial group in cases where there are no true generic words that embrace the group. *In re Schecter,* 205 F.2d 185, 189 (CCPA 1953). The Markush grouping was allowed because it was recognized that "where certain substances, which an inventor by experiment has found available for his purpose, fall within a generic group, but there is nothing to establish that all the species of that group have such similar characteristics as to make them available for this purpose, and there

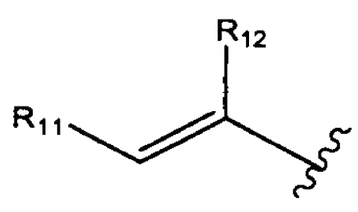
is no known subgeneric term which would include only the species found available." *In re Schecter* at 151 (quoting *Ex parte Burke* 21 U.S.P.Q. 399, 400 (1934)). The Markush grouping is proper when the substances grouped have a "community of chemical and physical characteristics" and that "inclusion in the group is not repugnant to scientific classification." *In re Jones,* 74 U.S.P.Q. 149, 151 (CCPA 1947). Such is the situation for the present invention. As discussed above, in the present case the compounds embraced by Formula V do have a "community of chemical and physical characteristics" and "inclusion in the group is not repugnant to scientific classification." The Examiner has not provided any evidence to the contrary.

In order to expedite prosecution of the patent, however, Applicants have amended independent claim 1, as agreed to in the interview on October 24, 2001, to recite Q as:

and ;

that G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;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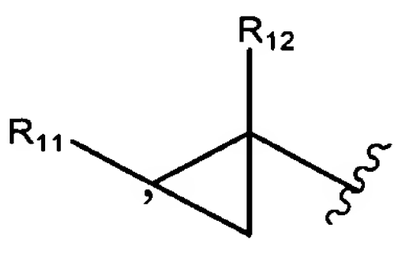
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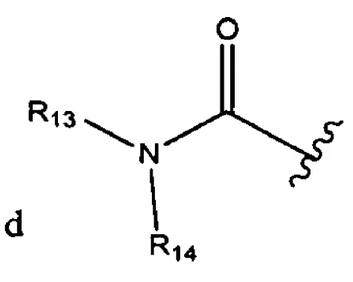

and ;

and that Z_1 and Z_2 is CH_2. Accordingly, Applicants respectfully submit that claims 1, 2. 4, 7-8, and 11 do define a proper Markush group. For the above reasons, Applicants respectfully request that the rejection of claims 1, 2, 4, 7-8, and 11 as being an improper Markush group be reconsidered and withdrawn.

THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 4-6 and 8-13 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement for the reasons set forth on page 3 of the Office Action. The Examiner alleges that

the specification does not provide enablement for treating any and all kinds of cancers, hyperproliferative cellular diseases, or diseases associated with angiogenesis. The rejection of claims 5-6, 9-10, and 12-13 directed to treating hyperproliferative cellular diseases or diseases associated with angiogenesis are rendered moot by the cancellation of those claims. With respect to claims 4, 8, and, 11, as amended, Applicants respectfully traverse the rejection. Claims 4, 8, and 11, as amended, are directed to treating specific cancers known to be treated by Taxol.

As discussed above, during the interview the Examiner restricted claims 4-6, 8-9, and 11-13 into three groups, Group I, claims 4, 7, 8, and 11 drawn to methods of treating cancer; Group II claims 5, 9, and 12, drawn to methods of treating a hyperprolferative cellular disease in a patient; and Group III claims 6, 10, and 13 drawn to methods of treating a disease associated with angiogenesis in a patient. Applicants have elected the claims of Group I for examination in this application and canceled the claims of Groups II and III. Accordingly, Applicants have limited the claims to recite cancers that are known to be treated by microtubule-stabilizing agents, which is recognized by the Examiner as treatable as in the case of Taxol®. Specifically, claims 4, 8, and 11, as amended, recite breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, melanoma, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, non-Hodgkin's lymphoma, multiple myeloma, prostrate cancer, bladder cancer, pancreatic cancer, and Karposi's sarcoma, all of which are known to be treated by Taxol® (*See, e.g.*, D.M. Bollag, Cancer Research, 55, No. 11, 2325-2333, 1995 (reference CC); G.H. Eltabbakh, Eur. J. Gynacol. Oncol., 20(1):18-9, 1999 ("Eltabbakh"); S. Glisson et al., Proc. Ann. Meet. Am. Soc. Clin. Oncol., 18:A814, 1999 ("Glisson"); G. Tortora et al., Cancer Res., 57,(22), 5107-11, 1997 ("Tortora"); E.K. Rowinski, Annu. Rev. Med., 48, 353-74, 1997 ("Rowinski"); K. Mross et al., Proc. Ann. Meet. Am. Soc. Clin. Oncol., 16:A776, 1997 ("Mross"); R. Panvichian et al., Proc. Ann. Meet. Am.Assoc. Cancer Res., 38:A1317, 1997 ("Panvichian"); R. Hajek, Cas. Lek. Cesk., 135(12), 393-6, 1996 ("Hajek"); D. Raghaven et al., Curr. Probl. Cancer, 19(1), 1-64, 1995 ("Raghaven"); L.A. Speicher et al., Cancer Res. 52(16), 4433-40, 1992 ("Speicher"); C.M. Spencer et al., Drugs, 48(5), 794-847, 1994 ("Spencer"); H.B. Newton, Expert Opin. Investig. Drugs, 9(12), 2815-29, 2000 ("Newton"); G.F. Fleming et al., J. Clin. Oncol., 19(4), 1021-9, 2001 ("Fleming");
http://health.yahoo.com/health/Drugs_Tree/Medication_or_Drug ("Yahoo"); and
http://oncolink.upenn.edu/pdq_html/6/engl/600715.html ("Oncolink")). Copies of Eltabbakh, Glisson, Tortora, Rowinski, Mross, Panvichian, Hajek, Raghaven, Speicher, Spencer, Fleming,

Yahoo, and Oncolink are enclosed herewith for the Examiner's convenience. Clearly, these cancers are fully enabled by the specification since the epothilones of the invention are known to exert a microtubule-stabilizing effect similar to Taxol® and hence have cytotoxicity against rapidly proliferating cells such as tumor cells (*See, e.g.*, Specification, page 1, lines 11-21 and page 8, lines 20-22).

Although now moot given our interview and agreement with the Examiner, Applicants note that while claims 4, 8, and 11 were rejected on the basis that the specification does not provide an enabling disclosure for the general treatment of cancer, the rejection is in essence a rejection for lack of utility since a rejection under the "how to use prong" of 35 U.S.C. §112 incorporates, as a matter of law, the specification disclose a practical utility for the invention. *In re Ziegler*, 992 F.2d 1197, 1200-01 (Fed Cir. 1993) and MPEP 2107 IV. Compliance with 35 U.S.C. §101 and §112, first paragraph, is satisfied if an Applicant has asserted any specific and substantial utility that is credible. MPEP 2107.01. Furthermore, assertions of utility in a specification are presumed to be true and "must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." MPEP 2107.01 (citing *In re Langer*, 503 F.2d 1380, 1391). To overcome the presumption Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. MPEP 2101.01 III, A.

In the present case Applicants have asserted that the claimed epothilone molecules can be used to treat cancers that are known to be treated by Taxol®. Moreover, this utility is clearly credible. One of ordinary skill in the art would readily recognize that epothilone derivatives would have this utility (*See, e.g.*, Bollag et al., *Cancer Research*, 55, 11 2325-33 ("Bollag"), reference CC on Form PTO 1449). Bollag discloses that epothilones A and B are mictrotubule-stabilizing agents having a neoplastic mechanism similar to that of paclitaxel (Taxol®). Clearly, one of ordinary skill in the art would find it credible that the claimed epothilone molecules would have a similar mechanism and could be utilized for the treatment of cancer and, in particular, for the treatment of the cancers specified in claims 4, 8, and 11, as amended, which are known to be treated by Taxol®. Thus, Applicants have complied with 35 U.S.C.§112, first paragraph, by asserting a specific and substantial utility that is credible. MPEP 2107.01. Moreover, the Examiner has failed to provide any factual basis or documentary evidence upon which it could be established that a person of ordinary skill in the art would not

consider the asserted utility as being credible to overcome the presumption of utility.

Importantly, Applicants note that they have not claimed a *cure* for cancer, which might raise the level of scrutiny to that being applied by the Examiner. MPEP 2107, IV, 2. Rather, Applicants have claimed a method for the *treatment* of cancer. The MPEP clearly states that "[t]he fact that there is no known cure for a disease, however, cannot serve as the basis for a conclusion that such an invention lacks utility" and that "[a]n assertion that a claimed invention is useful in treating a symptom of an incurable disease may be considered credible by a person of ordinary skill in the art on the basis of a fairly modest amount of evidence or support." MPEP 2107, IV, 2. The important point is that "[o]nly those claims for which an asserted utility is not credible should be rejected." MPEP 2107, IV, 2. Claims 4, 8, and 11, directed to a method of treating specific cancers is credible. For the above reasons, Applicants respectfully submit that claims 4, 8, and 11, as amended, are fully enabled and that the rejection under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

CONCLUSION

Applicants believes the application is in condition for allowance and earnestly requests reconsideration of the claims and allowance thereof. If the Examiner has any questions or suggestions to expedite allowance of this application, however, the Examiner is respectfully invited to call the undersigned to discuss the matter further.

An amendment fee of $576 is believed to be due for this submission for the addition of 32 dependent claims. Please charge the fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Paul E Dahl (45,627)

Date: October 29, 2001

35,203
Anthony M. Insogna (Reg. No.)

PENNIE & EDMONDS LLP
1667 K Street, N.W.
Washington, DC 20006
(202) 496-4460

Appendix A

Changes to the Specification for Application No. 09/084,542; filed May 26, 1998

The paragraph at page 8, line 20 to page 9, line 11 is revised as follows:

--The compounds of formula V are microtubule-stabilizing agents. They are thus useful in the treatment of a variety of cancers or other abnormal proliferative diseases, including (but not limited to) the following;

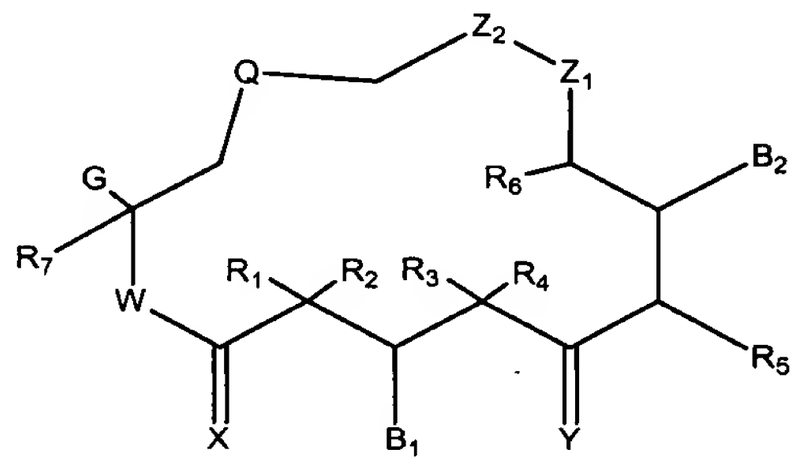
- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- [- tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;
- other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma, and glioma;]
- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and
- other tumors including melanoma, xenoderma, pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.--

Appendix B

Changes to the claims for Application No. 09/084,542; filed May 26, 1998

The rewritten claims were revised as follows:

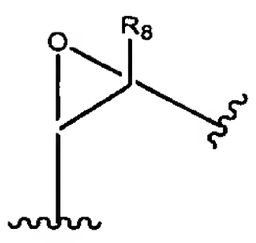
1. (Thrice amended) A compound of the formula



V

wherein

Q is selected from the group consisting of



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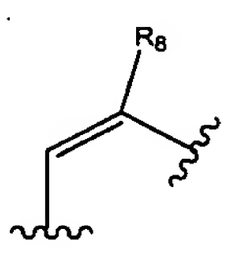

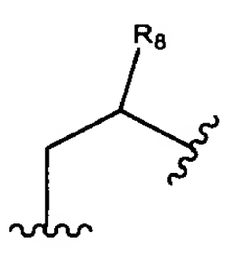

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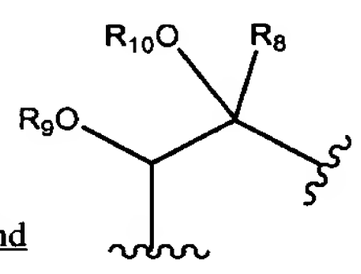

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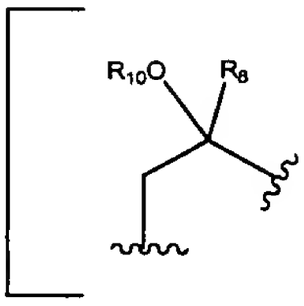

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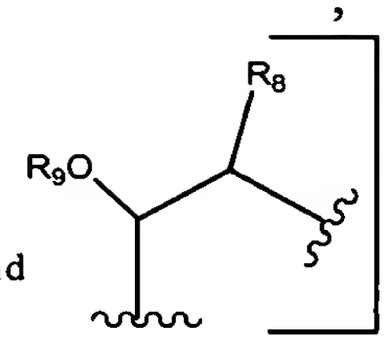
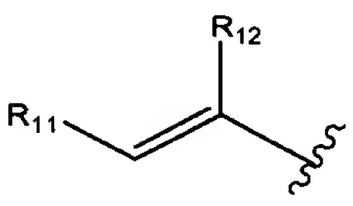


;

G is selected from the group consisting of alkyl[,]; substituted alkyl[,]; substituted aryl[,]; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; [heterocyclo,]



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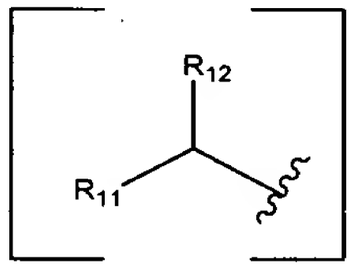

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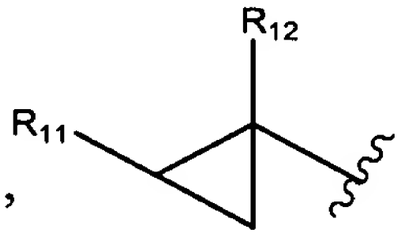

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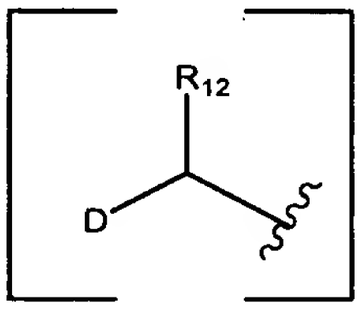

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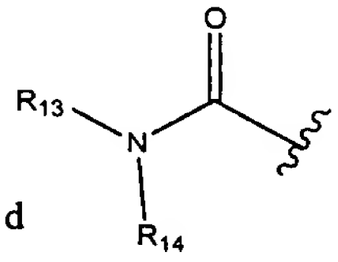


;

W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently [selected from the group consisting of] CH_2[, O, NR_{23}, S, and SO_2, wherein only one of Z_1 and Z_2 can be heteroatom];

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$, and when B_1 is H and Y is OH, H, they can form a six-membered ring ketal or acetal;

[D is selected from the group consisting of $NR_{28}R_{29}$, $NR_{30}COR_{31}$ and saturated heterocycle;]

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, $R_{32}C$=O, $R_{33}SO_2$, hydroxy, O-alkyl or O-substituted alkyl; and

the pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and steroisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

[Z_1 and Z_2 are CH_2; and]

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above

are excluded.

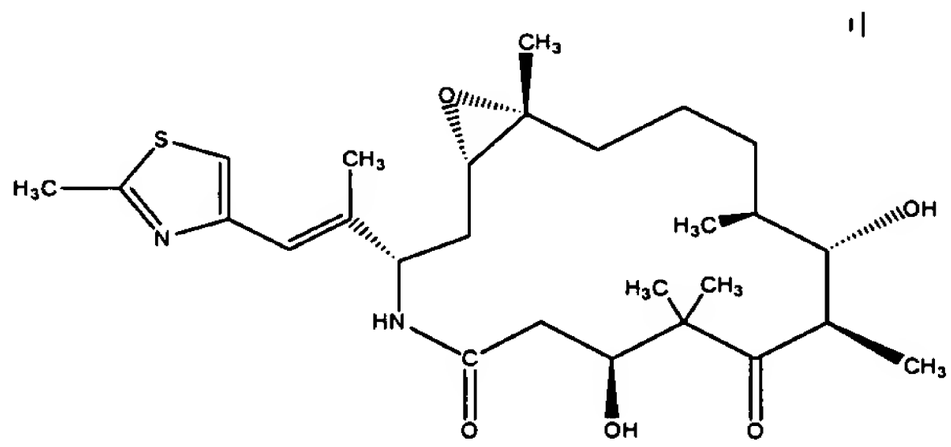
4. (Thrice amended) A method of treating <u>breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic</u> cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

7. (Amended) The method of claim 4, wherein the cancer is <u>cancer</u> [carcinoma] of the breast, ovary, or colon.

8. (Amended) A method of treating <u>breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic</u> cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

11. (Amended) A method of treating <u>breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic</u> cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

14. (Amended) The compound of claim 1 having the formula:

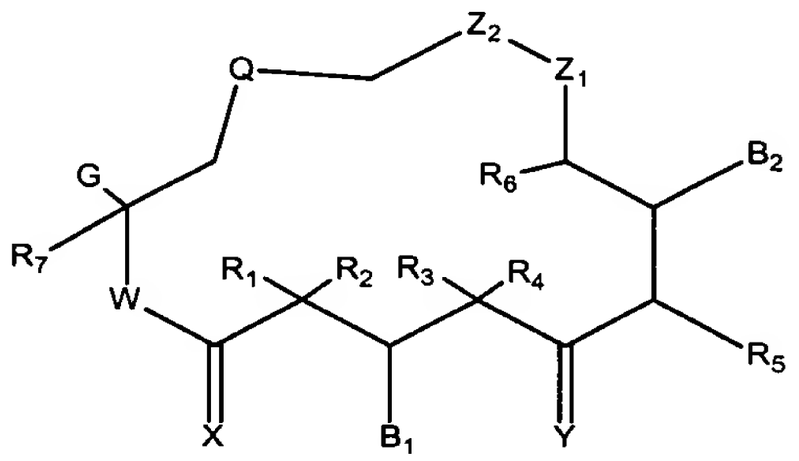


<u>or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer, optical isomer, or stereoisomer thereof.</u>

Appendix C

Pending claims for Application No. 09/084,542; filed May 26, 1998

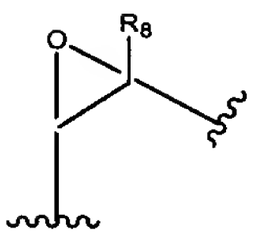
1. (Thrice amended) A compound of the formula

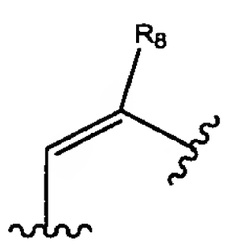


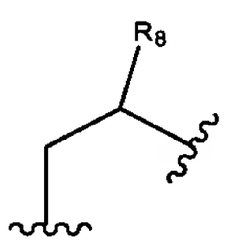
V

wherein

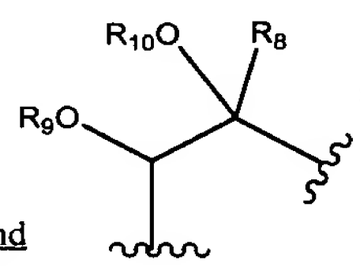
Q is selected from the group consisting of





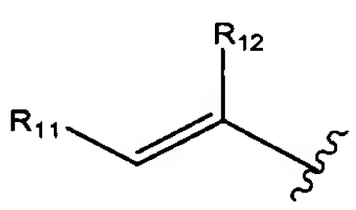


and



;

G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



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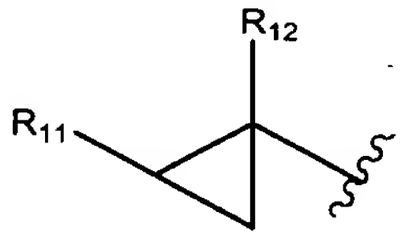
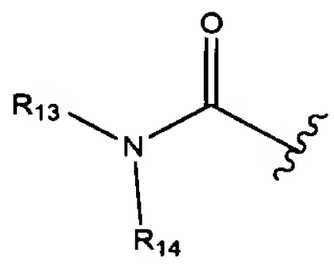


, and



;

W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$, and when B_1 is H and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, $R_{32}C$=O, $R_{33}SO_2$, hydroxy, O-alkyl or O-substituted alkyl; and

the pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and steroisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

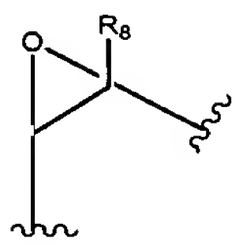
G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

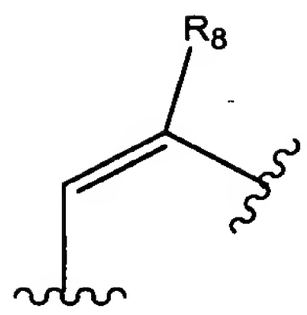
Q is as defined above

are excluded.

2. The compound of claim 1 wherein

Q is





X is 0;

Y is 0;

Z_1, and Z_2, are CH_2 and

W is NR_{15}.

3. A compound selected from the group consisting of:

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[4S-(4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[l-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7;9,13-tetramethyl-16-[l-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*1]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*1]-7,11-Dihydroxy-8,8,10,12,tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*1]-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*1]-7,11-Dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)fl-4,8-Dihydroxy-5,5,7,9,16-pentamethyl-16-]l-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(B),7R*,10S*,11R*,12R*,16S*1]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)etheny]]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)])-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-(1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]-7,11-Dihydroxy-4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[4.10]heptadecane-5,9-dione;

[4S-[4R*-7S*,8R,*9R-,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methy1-4-thiazolyl)ethenyl-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)1]-4,8-Dihydroxy-1,5,5,7,9-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,BR*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]1-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazoly)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,(E)]]-4,8-Dihydroxy,5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7, 11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazoly)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydxocymethy1-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;
and the pharmaceutically acceptable salts, solvates and hydrates thereof.

4. (Thrice amended) A method of treating breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial

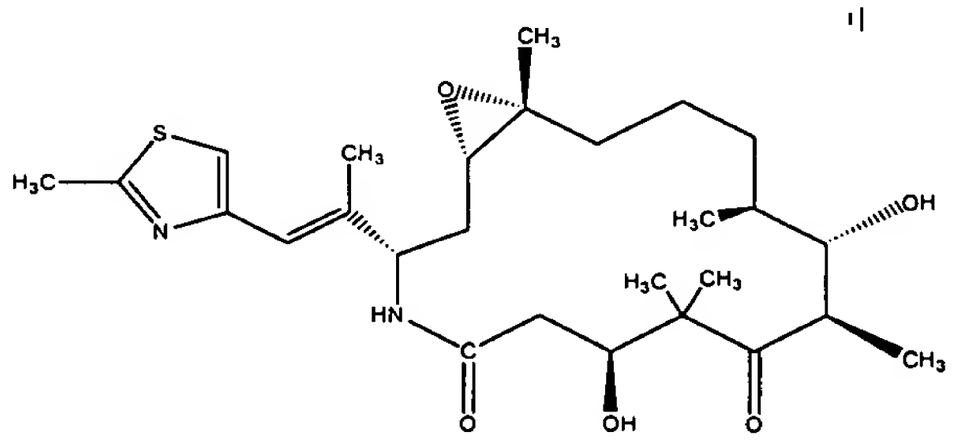
cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

7. (Amended) The method of claim 4, wherein the cancer is cancer of the breast, ovary, or colon.

8. (Amended) A method of treating breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

11. (Amended) A method of treating breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

14. (Amended) The compound of claim 1 having the formula:



or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer, optical isomer, or stereoisomer thereof.

15. (New) A method of treating breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said

treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.

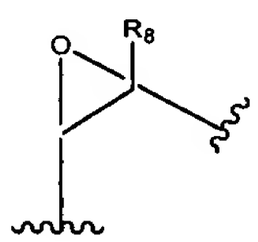
16. (New) The method of claim 15, wherein the cancer is cancer of the breast, ovary, or colon.

17. (New) The method of claim 8, wherein the cancer is cancer of the breast, ovary, or colon.

18. (New) The method of claim 11, wherein the cancer is cancer of the breast, ovary, or colon.

19. (New) The compound of claim 1, wherein G is 1-methyl-2-(substituted-4-thiazolyl) ethenyl group.

20. (New) The compound of claim 1, wherein Q is



21. (New) The compound of claim 1, wherein W is NR_{15}.

22. (New) The compound of claim 1, wherein X and Y are each O.

23. (New) A method of treating breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 19.

24. (New) The method of claim 23, wherein the cancer is cancer of the breast, ovary, or colon.

25. (New) A method of treating breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 20.

26. (New) The method of claim 25, wherein the cancer is cancer of the breast, ovary, or colon.

27. (New) A method of treating breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 21.

28. (New) The method of claim 27, wherein the cancer is cancer of the breast, ovary, or colon.

29. (New) A method of treating breast cancer, ovary cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 22.

30. (New) The method of claim 29, wherein the cancer is cancer of the breast, ovary, or colon.

31. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 1.

32. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 2.

33. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 3.

34. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 14.

35. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 19.

36. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 20.

37. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 21.

38. (New) A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 22.

39. (New) The method of claim 4, further comprising administering one or more of a additional anti-cancer agent.

40. (New) The method of claim 39, wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G_2-M phase.

41. (New) The method of claim 40, wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclase reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

42. (New) The method of claim 4, further comprising administering radiation therapy.

43. (New) A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable vehicle or diluent.

44. (New) A pharmaceutical composition comprising the compound of claim 2 and a pharmaceutically acceptable vehicle or diluent.

45. (New) A pharmaceutical composition comprising the compound of claim 3 and a pharmaceutically acceptable vehicle or diluent.

46. (New) A pharmaceutical composition comprising the compound of claim 14 and a pharmaceutically acceptable vehicle or diluent.

47. (New) A pharmaceutical composition comprising the compound of claim 19 and a pharmaceutically acceptable vehicle or diluent.

48. (New) A pharmaceutical composition comprising the compound of claim 20 and a pharmaceutically acceptable vehicle or diluent.

49. (New) A pharmaceutical composition comprising the compound of claim 21 and a pharmaceutically acceptable vehicle or diluent.

50. (New) A pharmaceutical composition comprising the compound of claim 22 and a pharmaceutically acceptable vehicle or diluent.

51. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

52. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

53. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

54. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.

55. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 19.

56. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 20.

57. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 21.

58. (New) A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 22.